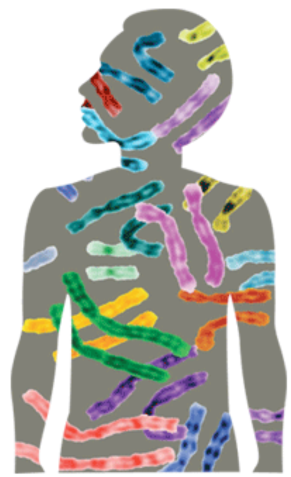
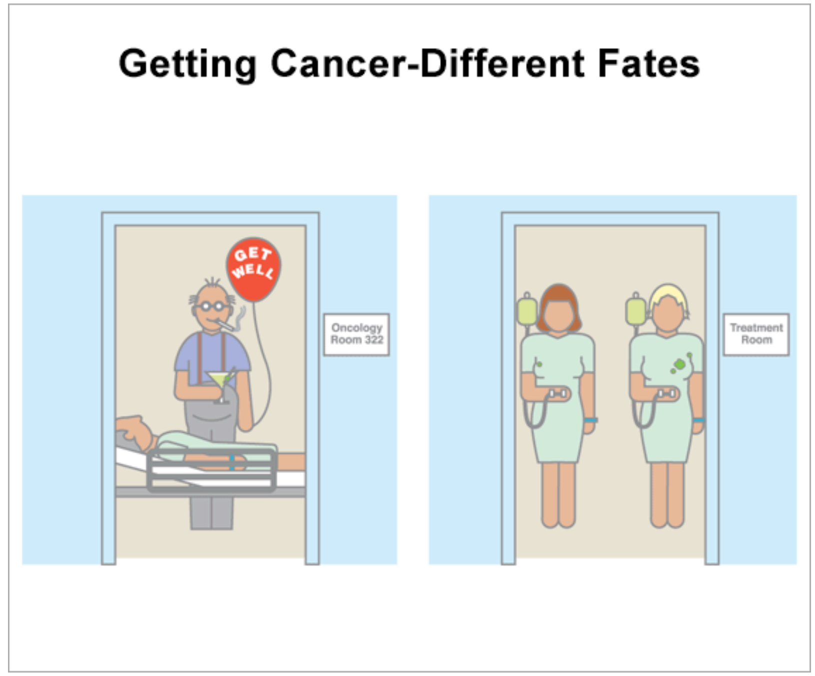
Introduction

While attention must be paid to the changes discovered within the genomic profile of a cancerous growth, equal attention must be paid to the intrinsic genetic background of each patient. Cancer does not develop in a vacuum, but within a patient, and each patient's distinctive genetic background results from both intrinsic and extrinsic factors.



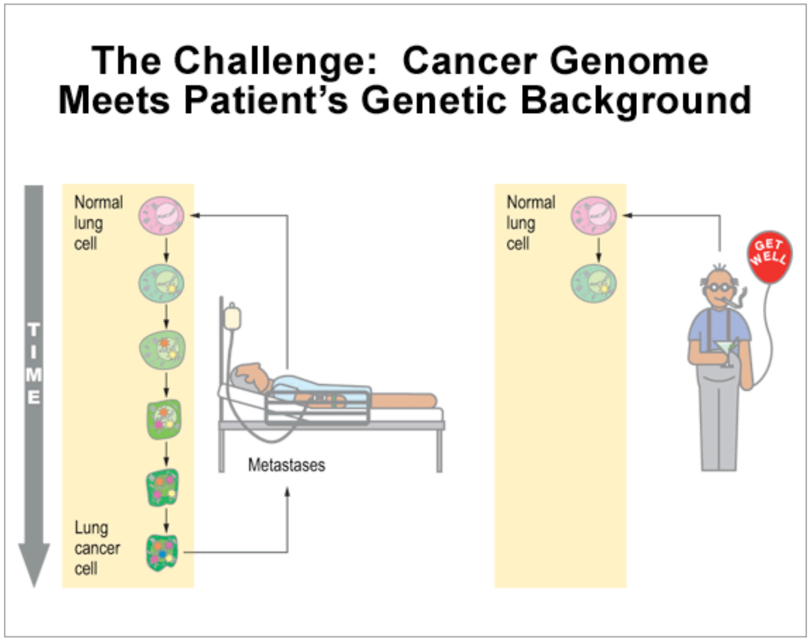
Getting Cancer-Different Fates

One man who smokes cigarettes lives to age 90 without getting lung cancer, while another man who smokes the same amount gets cancer at age 60. Why does one woman]s breast cancer respond to chemotherapy, and her tumor shrinks, while another woman's breast cancer shows no change after the same treatment? How can these differences be explained?



The Challenge: Cancer Genome Meets Patient's Genetic Background

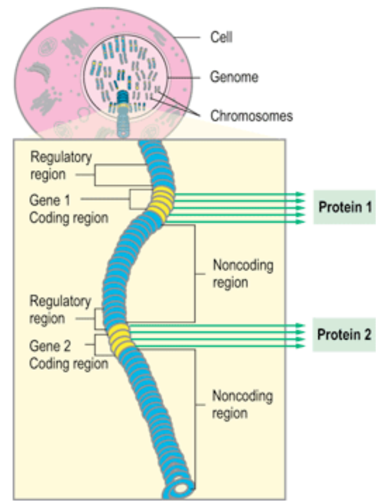
Differences observed among individuals in terms of their risk or response to chemotherapy point to the tremendous challenge involved in dealing with cancer, a disease of genomic instability. Even when a genome-wide profile of cancerous tissue reveals the molecular changes present there, the diagnosis is incomplete. Information about a person's medical history and genetic background also must be included in the case.



Human Genome and Coding Regions

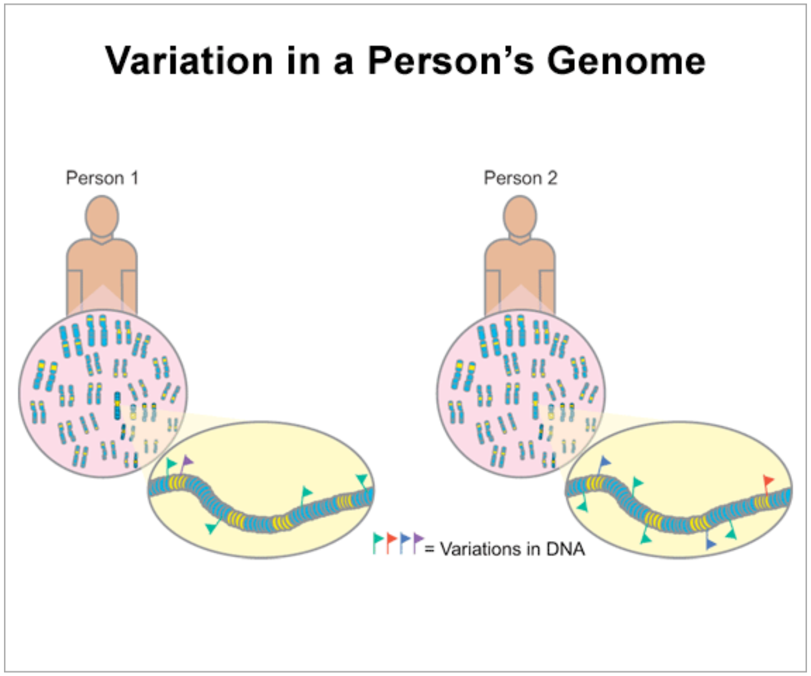
To understand a person's genetic background, one needs to start with the human genome, including all 25,000 genes.The human genome is the complete set of instructions for life as we know it. The human genome is located in the nucleus of every cell in the body, except for red blood cells, which have no nuclei. Only about 3 percent of this genome actually provides the set of instructions called genes that are used to build the body's proteins. These regions are called coding regions, and they are scattered throughout the chromosomes. In addition to coding regions, close to each gene are regulatory sequences of DNA, which are able to turn the gene "on" or "off." Scientists have discovered some functions for the remaining 97 percent of the genome, areas called noncoding regions, but most of this region remains a mystery.

Human Genome and Coding Regions



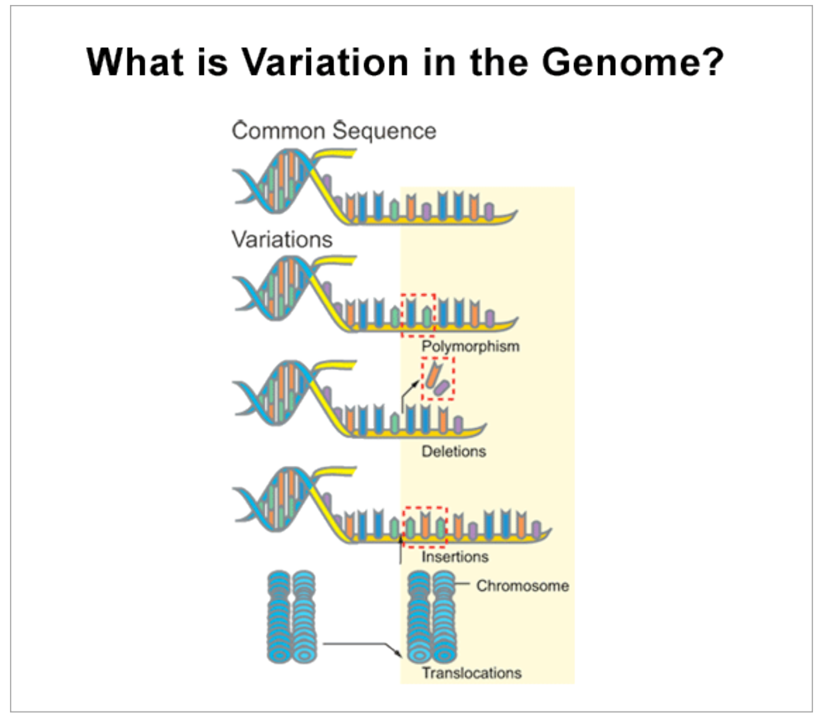
Variation in a Person's Genome

An amazing aspect of a person's genome is that there is so little variation in the DNA sequence when the genome of one person is compared to that of another. Of the 3.2 billion bases, roughly 99.9 percent are the same between any two people. It is the variation in the remaining tiny fraction of the genome, 0.1 percent—roughly several million bases—that plays a powerful role in deterring or encouraging cancer.



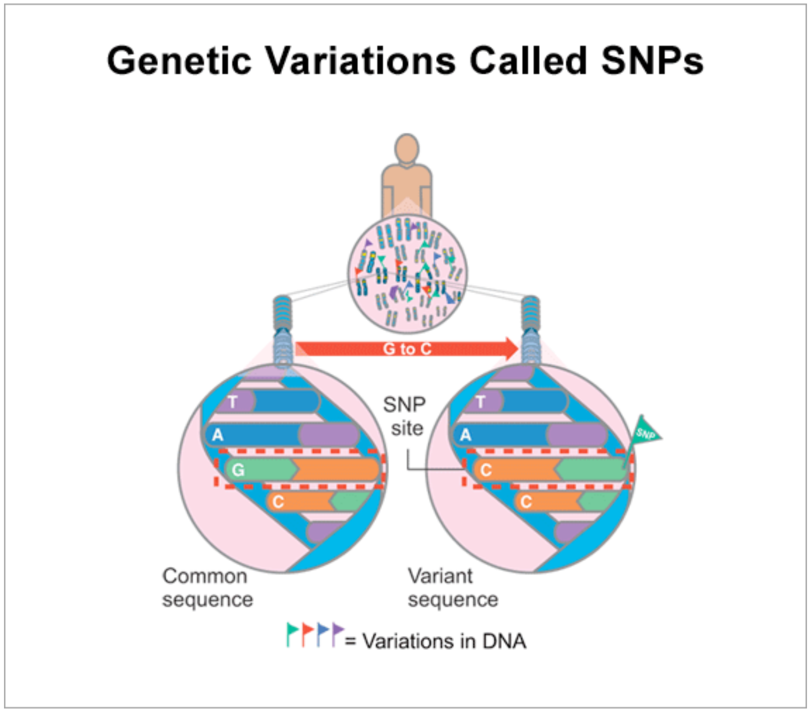
What is Variation in the Genome?

Variation occurs whenever bases in a person's DNA sequences change. Variations can involve only one base, many bases, or even large segments of chromosomes. If the two strands of a chromosome are thought of as nucleotides threaded on a string, then, for example, a string can break, resulting in a re-ordering of the beads. One or more nucleotides may be changed, added, removed, or exchanged. In chromosomes, these changes are called polymorphisms, insertions, deletions, or translocations.In addition to these changes, some persons have DNA sequences called "repeats" that like to insert extra copies of themselves several times. Chromosomes can also undergo more dramatic changes called translocations. These occur when an entire section of DNA on one chromosome switches places with a section on another. Not all variations in a person's DNA sequences have an effect. Among the variations that do cause effects, some are more serious than others. The outcome depends on two factors: where in the genome the change occurs (i.e., in a noncoding, coding, or regulatory region) and the exact nature of the change.



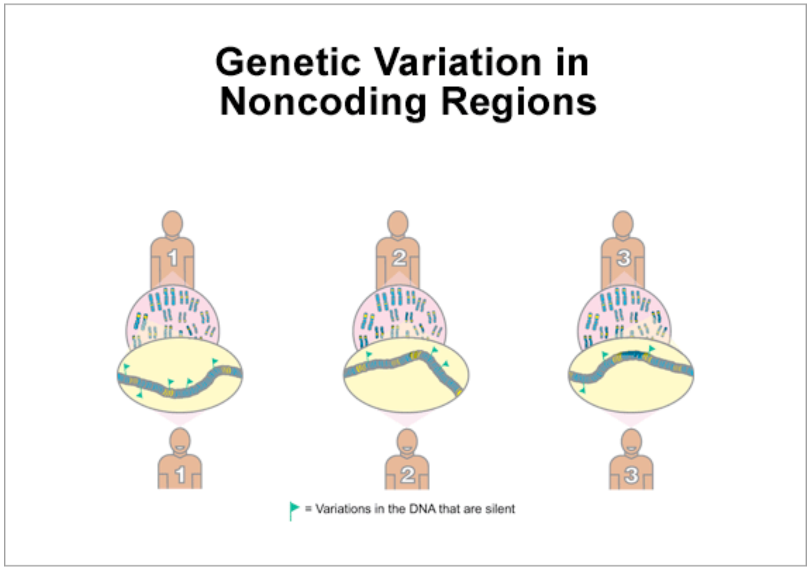
Genetic Variations Called SNPs

Cancer researchers think that, in addition to inherited or acquired mutations, tiny variations in a person's genome called single nucleotide polymorphisms, or SNPs ("snips") for short, may play a role in cancer. A SNP is defined as a single base change in a DNA sequence that occurs in a significant proportion (more than 1 percent) of a large population. The single base is replaced by any of the other three bases. Here is an example: In the DNA sequence TAGC, a SNP occurs when the G base changes to a C, and the sequence becomes TACC. SNPs are scattered throughout a person's genome and are found in both coding AND noncoding regions. They can cause silent, harmless, harmful, or latent effects. They occur with a very high frequency, with estimates ranging from about 1 in 1000 bases to 1 in 100 to 300 bases. This means that there could be millions of SNPs in each human genome.



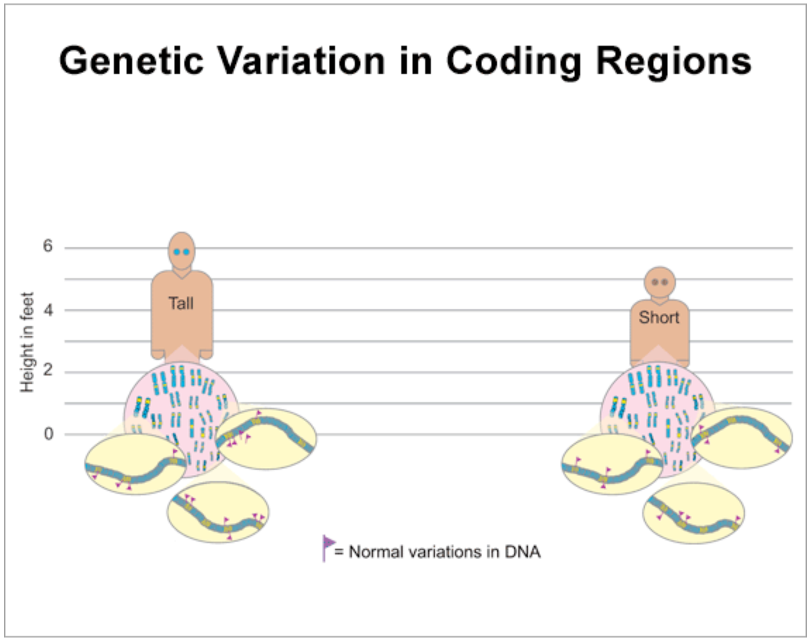
Genetic Variation in Noncoding Regions

Most SNPs occur in noncoding regions and do not alter genes. So most variations in the human genome have no known effect at all because they occur in noncoding regions of the DNA. In addition, there are some changes that do occur in coding and regulatory regions, yet the effect is not entirely understood. All these are silent variations.



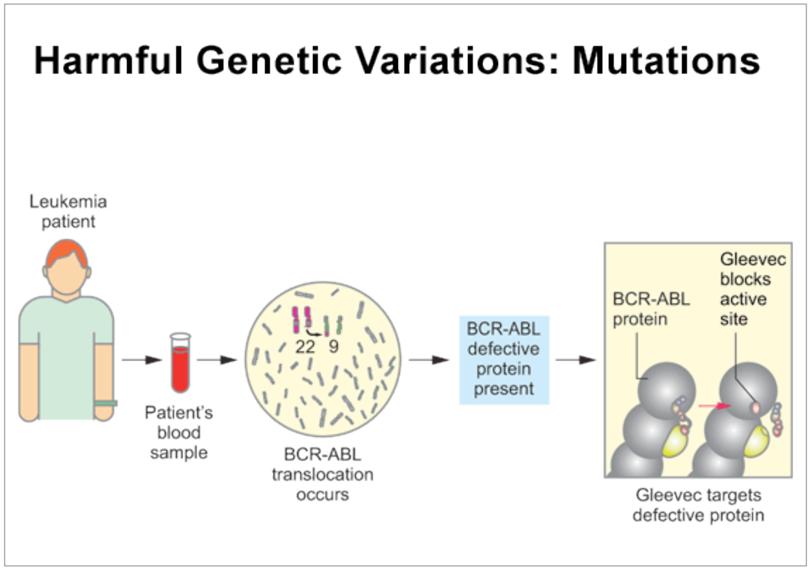
Genetic Variation in Coding Regions

The remaining SNPs occur in coding regions. They may alter the protein made by that coding region, which in turn could influence a person's health. Some of the variations that occur in the coding and regulatory regions of genes simply contribute to the normal variation observed among people. They can, for example, change the way a person looks. Some people have blue eyes, others brown; some are tall, others short. Other variations in coding regions are harmless because they occur in regions of a gene that do not affect the function of the protein made.



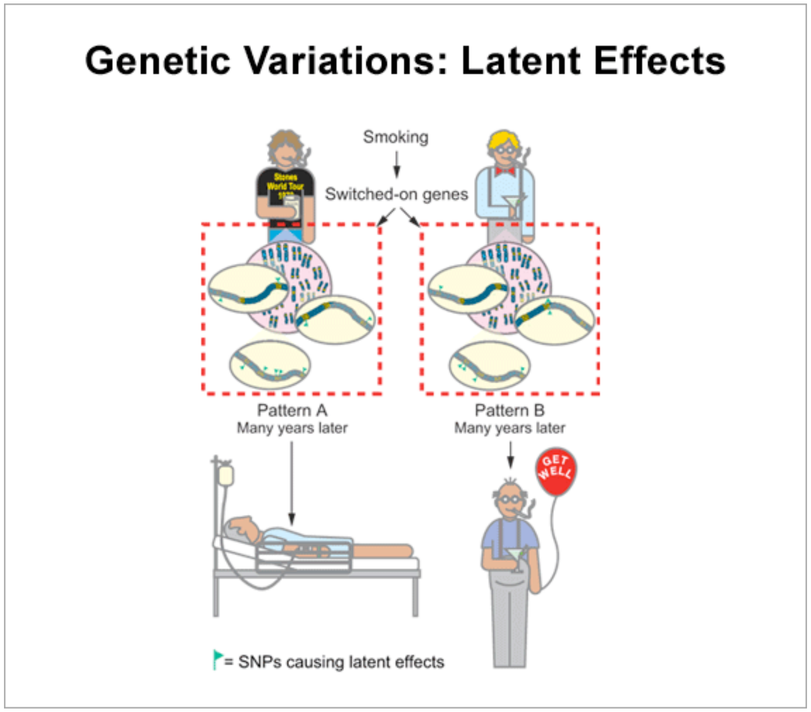
Harmful Genetic Variations: Mutations

There are a group of variations in coding and regulatory regions that result in harmful effects. These are called mutations. Mutations alter the gene's instructions for its corresponding protein. If many such variations occur in critical genes within the same cell, cancer may develop. In chronic myelogenous leukemia, a translocation occurs between chromosome 9 and 22. This rearrangement of genomic material creates a fusion gene called *Bcr-Abl* that produces a protein (tyrosine kinase) thought to promote the development of leukemia. The drug Gleevec blocks the activation of the Bcr-Abl protein.



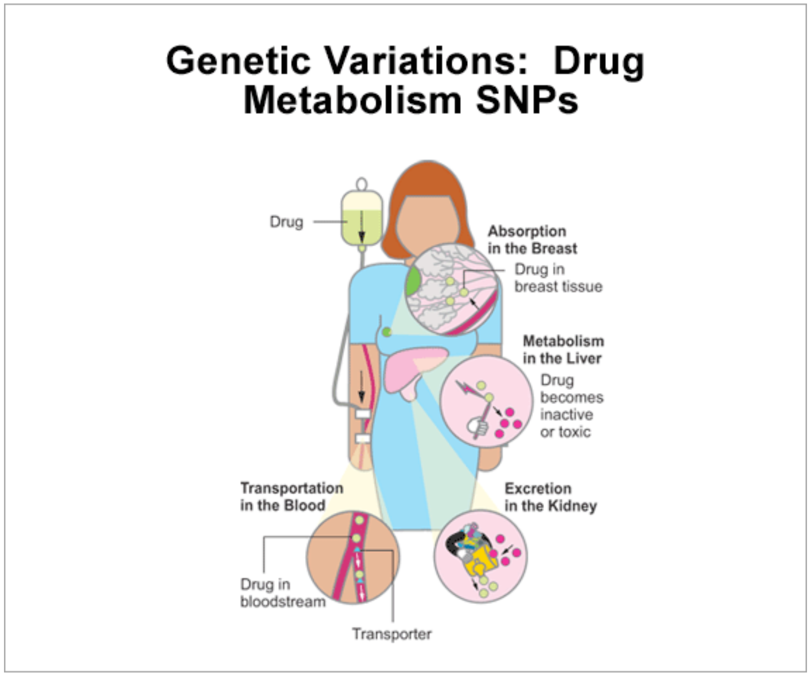
Genetic Variations: Latent Effects

An individual may also harbor genetic variations that have "latent" effects. These variations, found in coding and regulatory regions, may have small effects on their own, but over time, in the context of other genetic changes, infections, or environmental exposures, they may eventually alter a person's risk for cancer. They may also explain why one person responds to a drug while another does not. These variations are very difficult to study, but populations studies are attempting to unravel their effects. Here is part of the genome from two people who are both smokers, but only one of them gets cancer. The zoom into the chromosomes of these two men shows just a sampling of the differences in variation that are responsible for their individual cancer risk. The variations themselves do not cause cancer. They only affect each person's susceptibility to the damaging effects of tobacco smoke after exposure.



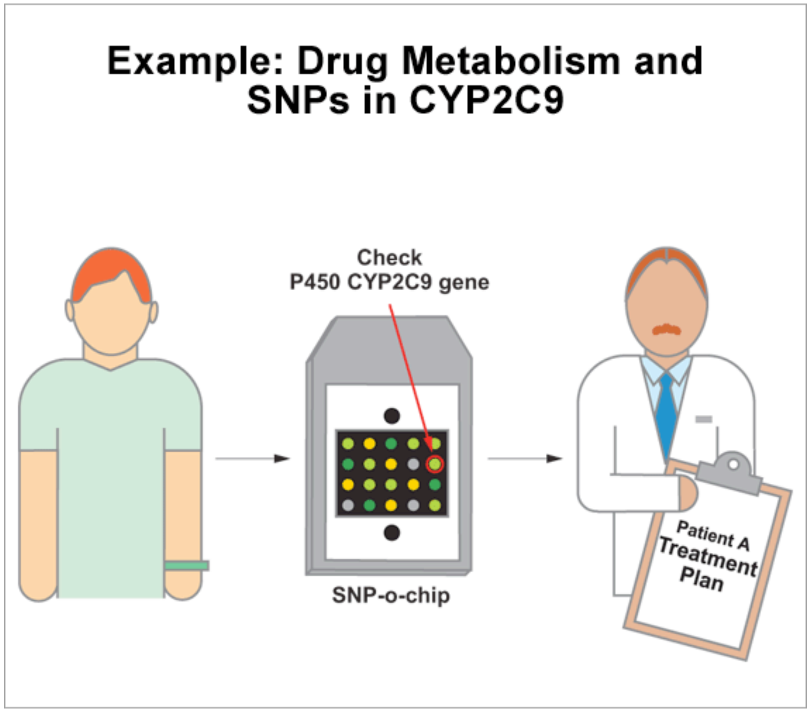
Genetic Variations: Drug Metabolism SNPs

When a person takes medication, many proteins in his or her body interact with the drug as it is transported throughout the body, absorbed into tissues, metabolized into more active forms or toxic byproducts, and excreted. If an individual has SNPs in any one or more of these proteins, they may alter the time the body is exposed to active forms of a drug or to any of its toxic byproducts. Researchers now have the tools to study how genetic variations can influence an individual person's response to a drug. They can even capture information on metabolism-related genetic variations that occur among different genders or ethnic groups. The data they are collecting should help to explain why certain persons within a person population may have different side effects in response to the same drug or some may respond to therapy better or worse than others.



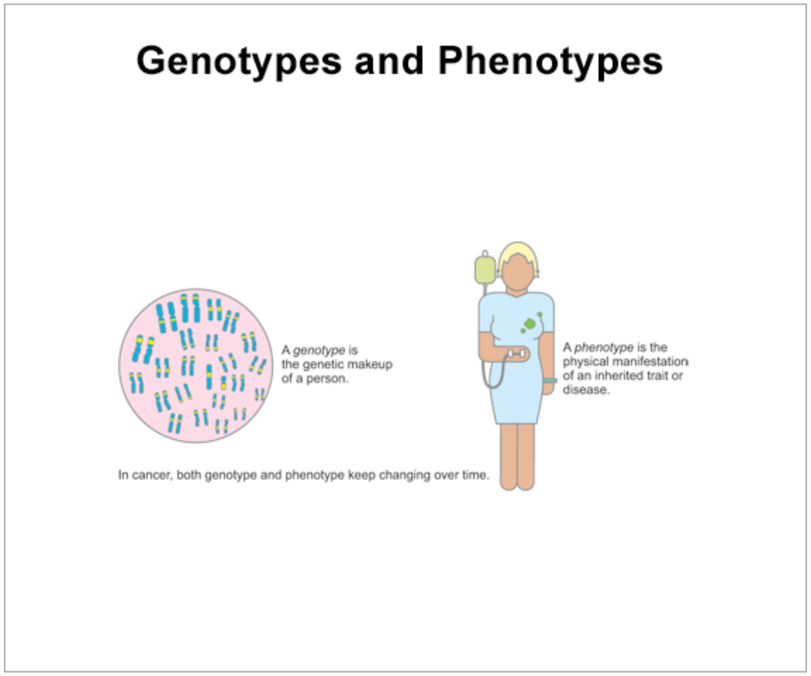
Example: Drug Metabolism and SNPs in CYP2C9

CYP2C9 genetic variants are a good example of how SNPs can be linked to abnormal drug metabolism. CYP2C9 is an important cytochrome P450 protein that works in the liver to metabolize drugs. Genetic variation in the gene for this protein can alter this metabolism. As many as 40 percent of persons carry a SNP that produces a deficient CYP2C9 protein. Deficiencies in this protein can impair the metabolism of as many as 1 in 5 medications currently on the market. Fortunately, technology makes it possible for a person to discover the drug metabolism variants that he or she carries. This information can then inform drug selection.



Genotypes and Phenotypes

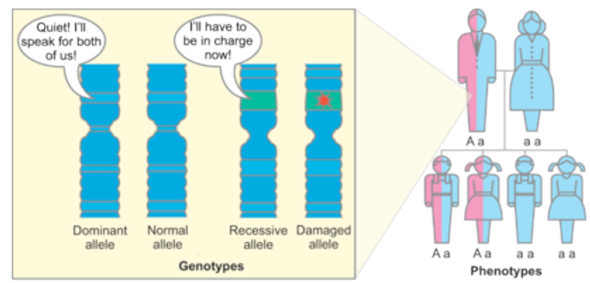
In order to understand some additional contributors to a person's genetic background, one must understand terms like genotype, phenotype, and alleles. Cancer may start as a new genotype, that is, as a change in the genetic makeup of a person, but it ultimately produces a new phenotype as well. A phenotype is the physical manifestation of a genotype in the form of a trait or disease. Cancer is known for its ever-changing genotypes and phenotypes.



Genotypes, Phenotypes and Alleles

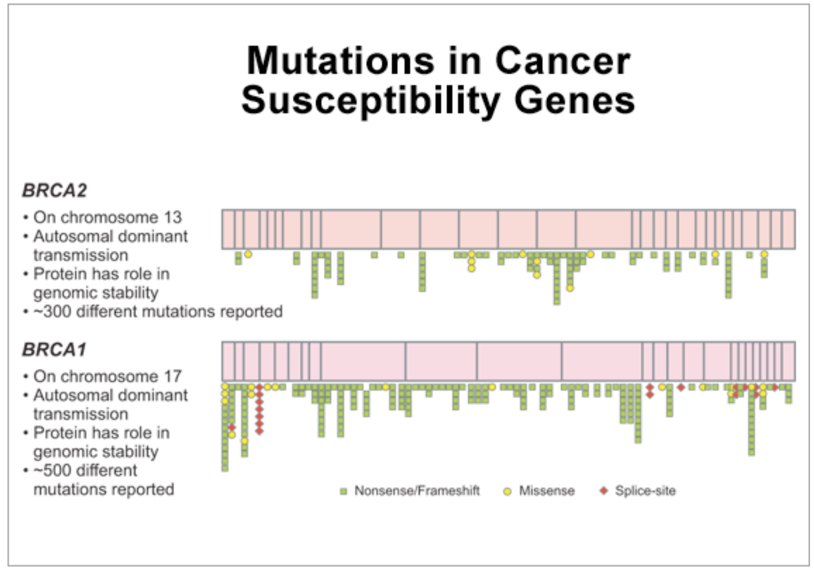
All genotypes are not created equal in their influence on phenotype. Genes come in many varieties called alleles, and some are more dominant than others. In a pair of alleles, the effect of a dominant allele prevails over the effect of a recessive allele. And the effects of a recessive allele become apparent only if the dominant allele becomes inactivated or lost.

Genotypes, Phenotypes and Alleles



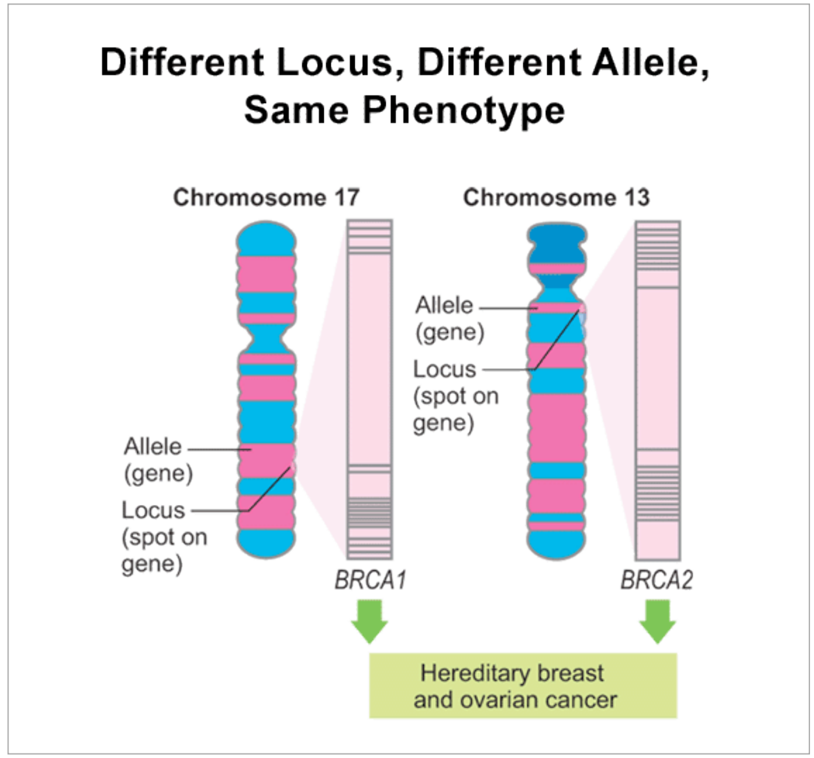
Mutations in Cancer Susceptibility Genes

Now let's look at what a difference an allele can make. Another contributor to cancer risk comes from cancer-predisposing germline mutations called cancer susceptibility genes. Persons with susceptibility mutations carry these altered alleles in every cell in their bodies. Here are examples of the mutations seen in the BRCA2 and BRCA1 breast cancer susceptibility genes. Inheriting these mutated alleles greatly increases a person's lifetime cancer risk. This may explain why cancers linked to germline mutations in susceptibility genes often occur at an earlier age and in multiple sites.



Different Locus, Different Allele, Same Phenotype

Many cancer susceptibility syndromes are genetically heterogeneous (a mixture), which means that different mutations (genotypes) can be expressed as the same phenotype (e.g., cancer). These different mutations may be located within the same gene but at different locations (locus heterogeneity) or on different genes altogether (allelic heterogeneity). For example, hereditary breast and ovarian cancer susceptibility has both locus and allelic heterogeneity. More than 500 different mutations have been identified that can occur in the BRCA1 gene on chromosome 17 and increase a woman's risk for breast cancer. And more than 300 mutations scattered throughout the BRCA2 gene on chromosome 13 are associated with hereditary breast and ovarian cancer susceptibility.



Incomplete Penetrance

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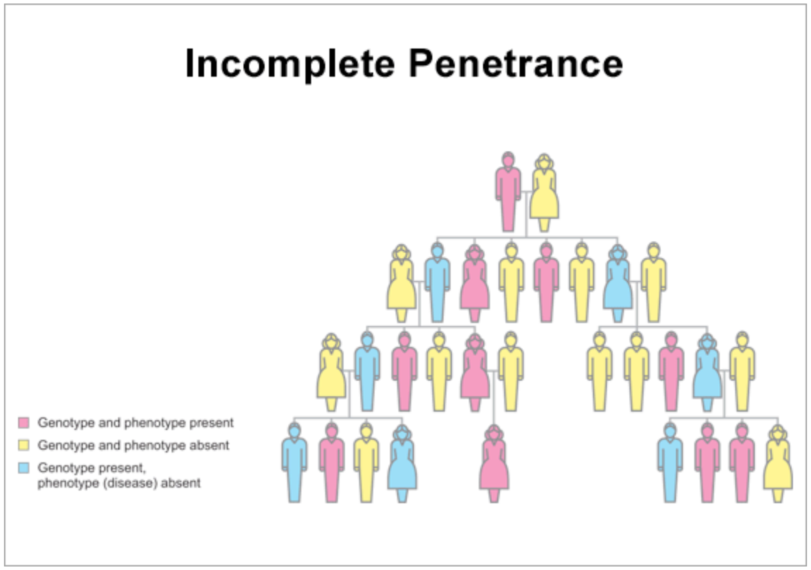
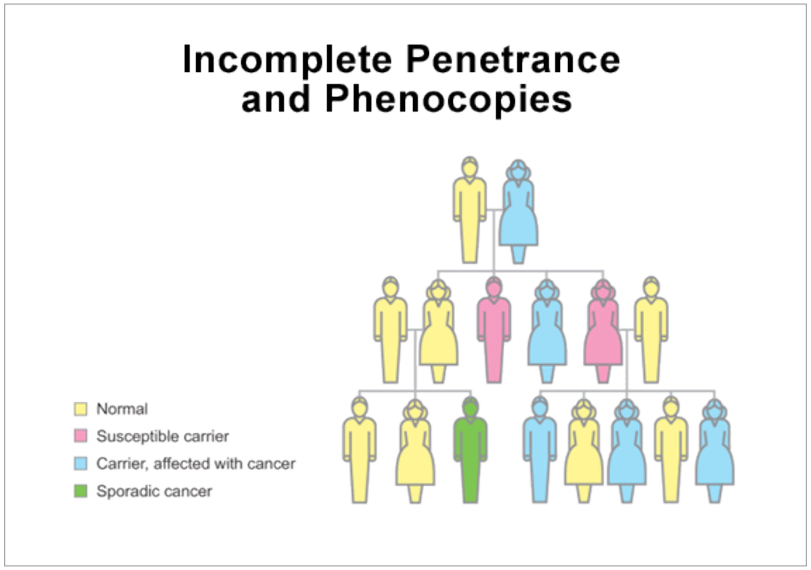


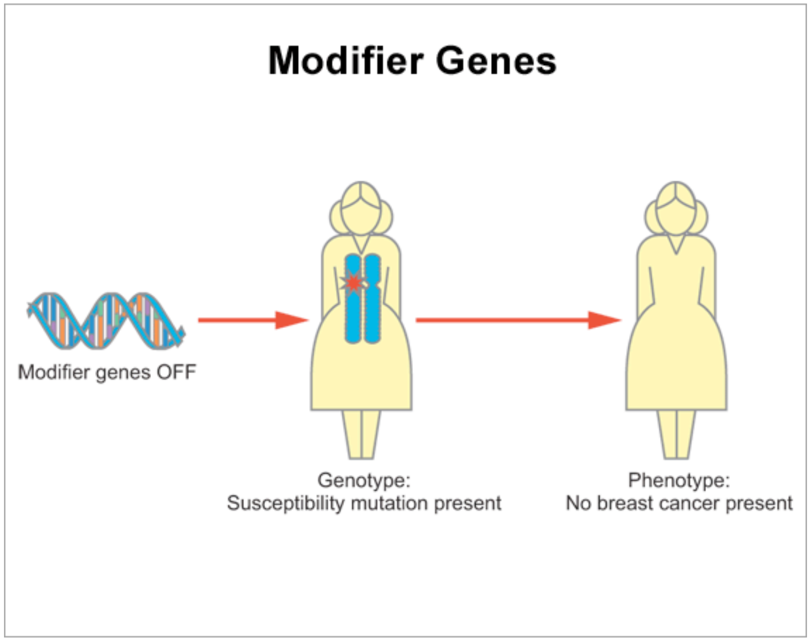
Incomplete Penetrance and Phenocopies

Individuals who inherit cancer susceptibility mutations inherit a predisposition to cancer, not cancer itself. Some mutation carriers inherit their predisposing genotypes in an autosomal dominant fashion, yet they do not develop cancer because their altered genes are incompletely penetrant.Further confusing the situation is the fact that sporadic forms of cancer may also occur in families along with a hereditary cancer syndrome. These cases of sporadic cancer are called phenocopies because their phenotype is similar to that of the affected mutation carriers, but their genotype is different. Genomic profiling of normal and cancer cells from the same person can determine if the cancer is hereditary or sporadic in nature.



Modifier Genes

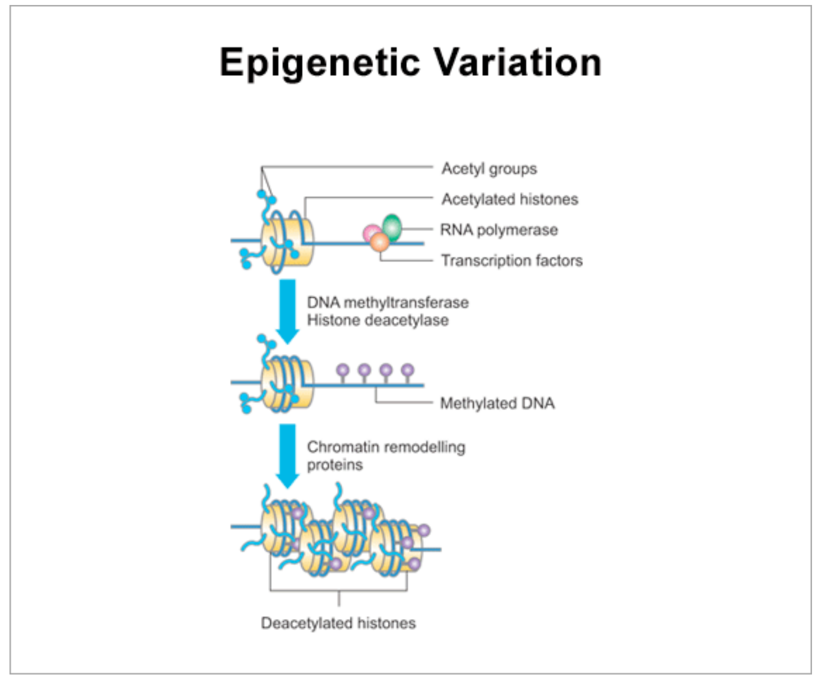
One explanation for the incomplete penetrance seen in persons who have inherited cancer susceptibility genes may lie in the effects of modifier genes. Modifier genes are simply genes that indirectly influence the expression of other genes. One can think of the modifier gene as a breaker switch, which controls all of the power. If the breaker switch is off, it doesn't matter whether the susceptibility gene is ready to turn on or not. There is no power, so it won't work. If both copies of modifier genes lead to a breaker switch being thrown, then the gene for cancer susceptibility will be silenced. On the other hand, if the modifier genes power up to let the cancer susceptibility gene be expressed, then there still must be a functioning copy of the gene available. Here the switch has been thrown OFF by modifier genes and the cancer susceptibility gene is silenced.



Epigenetic Variation

Reversible, heritable changes called epigenetic factors also can indirectly regulate gene expression and protein production. These modifications can occur even without a change (mutation) in a gene’s DNA sequence. Epigenetic alterations may be induced spontaneously, in response to environmental factors, or may simply be part of a person’s genetic background. Some examples include:

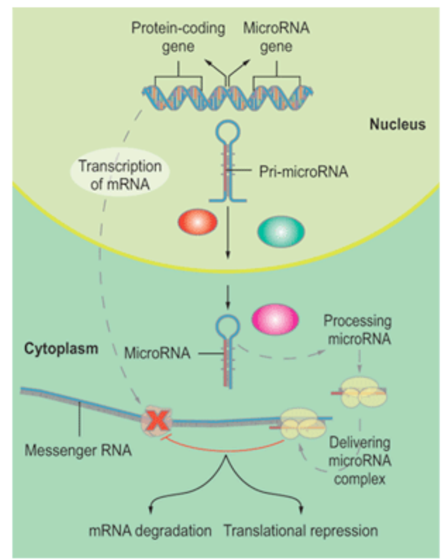
- Addition of a methyl group to CpG dinucleotides, which are special regions in DNA bases where gene activity can be silenced when methyl groups are attached
- Removal of acetyl groups from histone tails, which stops the gene activity of the DNA bases wrapped around the histone, causing the DNA to coil up tightly.



The Role of MicroRNAs

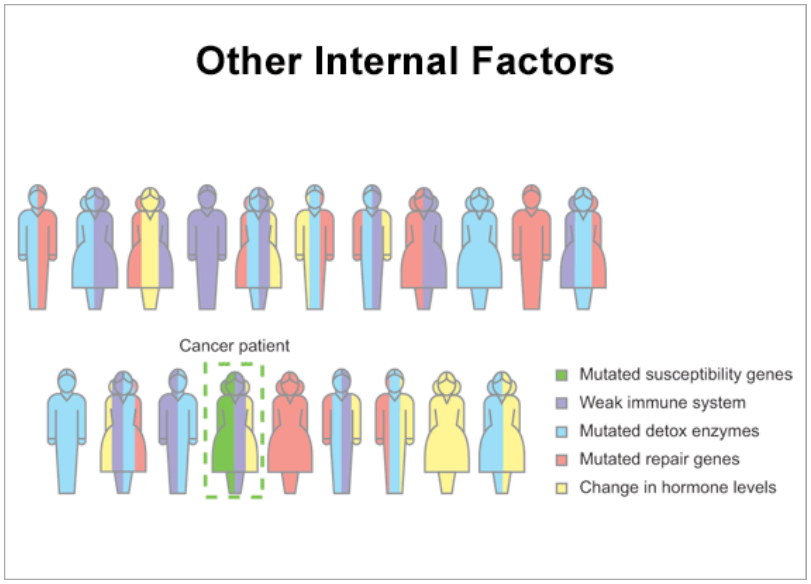
MicroRNAs also can indirectly interfere with gene expression in a person. These small RNA molecules play an important role in controlling gene activity by regulating a process known as translation. In translation, another type of RNA molecule, called a messenger RNA, which is produced by copying the genetic code of a gene, is used as a template to make proteins. There are many different types of microRNAs, and a single microRNA species can affect the expression of many different proteins. Changes in microRNA levels have been linked to several human cancers.

The Role of MicroRNAs



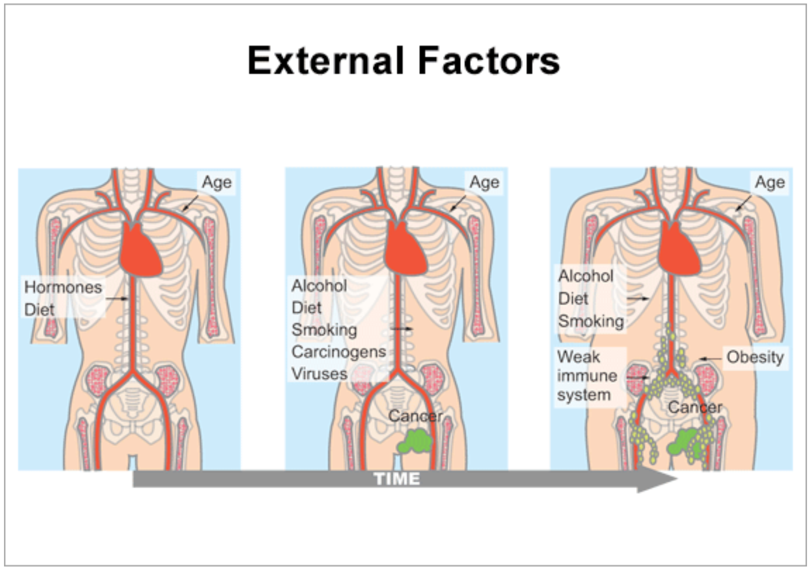
Other Internal Factors

Clearly, other factors are involved in cancer that we still do not understand. Some families are more cancer prone than others. In part, inheritance is involved in some of these cases. This is because, at birth, some offspring unknowingly inherit gene changes that can make them more susceptible to cancer. But this explains only a very small percent of new cancer cases, no more than 5 percent. Others factors that may change cancer risk include having stronger or weaker immune systems, variations in detoxifying enzymes or repair genes, or differences in hormone levels.



External Factors

A cancer patient's genetic background may be impacted by external factors as well. Over a lifetime, a person's internal genetic makeup persistently interacts with many external factors such as diet, smoking, alcohol use, hormone levels, or exposures to certain viruses and cancer-linked chemicals (called carcinogens). These may collectively conspire with internal genetic changes to destabilize normal checks and balances on the body's growth and maturation. (Please see Understanding Cancer and the Environment for more information.)



Still Don't Completely Understand

We don't know which specific combinations of environmental factors on the outside of a person's body combines with an individual's genetic background on the inside to cause cancer. We don't know why two persons can have very similar environmental exposures, yet one gets cancer and the other does not. A number of individual factors are involved, and there are complex relationships among them. Hopefully, the technology that is empowering an era of personalized medicine will also help oncologists to address these and other unanswered questions about cancer.